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EVALUATION OF PERMANENT IMPLANTATION OF ELECTRODES WITHIN THE BRAIN [1]

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INTRODUCTION

Permanent implantation of electrodes within the brain of animals allows the study of many cerebral functions for long periods of time without the handicap of anesthesia. Two methods have been used by several investigators:

1. The remote control technique, in which a receiver is placed beneath the skin, with the terminal leads ending in the brain substance (Chaffee and Light 1934; Clark and Ward 1937; Fender 1937; Gengerelli and Kallejian 1950; Harris 1946; Loucks 1934; Mauro *et al.*, 1950; Verzeano and French 1953). The receiver is activated by induction or by radio and there are no leads between the stimulator and the animal. Some limitations of the technique will be discussed later.

2. In the other techniques, electrodes are implanted within the brain; the terminals, through which the animals are connected for stimulation or recording, remain outside the scalp (Bradley and Elkes 1953; Clark and Ward 1937; Delgado 1952a; Emerson *et al.* 1955; Epstein 1949; Gastaut 1951; Heath *et al.* 1954; Hess 1932; Hoagland 1940; Hunter and Jasper 1949; Ingram *et al.* 1951; Jung and Kornmüller 1938; Kaada 1951; Knowles 1951; Koella *et al.* 1951; Lewandowsky 1903; Lilly *et al.* 1952; Livanov and Poliakov 1945; Lubinska and Konorski 1939; Masserman 1941; Old and Milner 1954; Pacheo and Delmas-Marsalet 1924; Rheinberger and Jasper 1937; Sawa *et al.* 1953). Some technical details will also be discussed later.

In the last few years cerebral implantation of electrodes has also been used in human patients (Bickford *et al.* 1953; Brazier *et al.* 1954; Delgado *et al.* 1952; Heath *et al.* 1954; Henry 1949; Pool and Clark 1954; Shimazono *et al.* 1954; von Baumgarten 1953). The technique of implanting electrodes in animals that we have been using for the past seven years (Delgado 1949) may have some advantages and it is described and commented on in the present paper.

Construction of needle electrodes (fig. 1). Stainless steel wire, .005" diameter, covered by quadruple teflon (Hitemp Wires, Inc., Mineola, New York) was used. Five pieces of decreasing length (e.g. 97, 94, 91, 88 and 85 mm.) were cut and straightened by stretching between two hemostats. Another piece of teflon coated stainless steel wire, .007" diameter, about 100 mm. long, was cut. Both ends of each wire were scraped free of insulation, 5 mm. at the top and 1 mm. at the tip. A small ball was made at the 1 mm. end of the .007" wire by means of an electric arc (Riley 1949). This ball constitutes the tip of the electrode. The 6 wires were cemented together with plexiglas dissolved in dichloroethylene, spacing the 1 mm. bare tips 3 mm. apart (the distance between the tips of the leads was determined by the topography of the cerebral structures involved in the experiment). The group of wires was protected by a tube of polyethylene (PE 90, Clay-Adams) which was closed at both ends by means of heat. The 5 mm. bare ends of all the wires were soldered in an identifiable order to a subminiature 7 pin socket, similar to those used in hearing aids. Then a double piece of bare stainless steel wire, .020" diameter and about 100 mm. long was soldered to pin no. 4; this wire anchored the electrode to the skull and was also used as reference lead in monopolar stimulation or recording. The leads were tested with an ohmmeter to check position and insulation. The base of the socket, with all the joints, was then covered with insulation enamel (E-33 clear, Insl-X Co., Ossining, New York).

Variations in construction: in some experiments silver wire of the same diameter and insulation was used to construct the needle electrodes, which were then very flexible. Their advantage was that they followed any brain movement, but they had no rigidity. Therefore, for introduction into the brain,

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it was necessary to use .3 mm. diameter stainless steel tubing which held a tiny hook made at the tip of the needle. The tube was then removed, leaving the electrode in position.

Construction of plate electrodes (fig. 1). A piece of polyethylene sheet (1 mill thick), about 30 × 4 mm., was cut. Six small needle holes, 5 mm. apart, were punched in the middle of the sheet along the length. Six pieces of silver wire (100, 95, 90, 85, 80 and 75 mm. long), .005" diameter, covered by quadruple teflon, were cut; one end of each piece was scraped for about 5 mm.; a small ball was made on the other end by means of a flame; the balled tips were then threaded through the holes in the polyethylene sheet. The under side of this plate was covered by another piece of the film and both pieces fused by means of heat (an electric flatiron was used). The silver wires above the plate were cemented together with plexiglas dissolved in dichloroethylene, and a short piece (about 30 mm.) of polyethylene tubing (PE 90) pulled over them for protection. The other ends of the wires were soldered in identifiable sequence to a 7 pin subminiature socket. A bare stainless steel wire, .020" diameter, was soldered to pin no. 4. This heavy wire anchored the plate electrode to the skull. The leads were tested with an ohmeter to check position and insulation. The base of the socket and all the soldered joints were coated with Insl-X E-33.

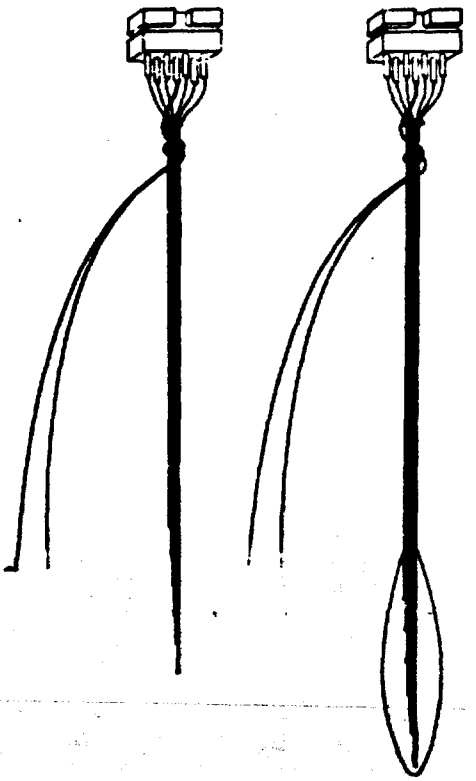

Fig. 1
Diagram of plate and needle electrodes.
The actual diameter of the shaft is about 0.5 mm.

Sterilization. For use in animals the electrodes were washed with soap and water and immersed in Zephiran 1:1000 for one to two hours. This has proved to be sufficient. For use in human patients the needle electrodes were autoclaved and the plate electrodes immersed in Zephiran overnight.

Method of implantation (monkeys). The animals were operated upon under Nembutal anesthesia, with aseptic precautions. After shaving the head, the monkey was placed in a Horsley-Clarke instrument. An incision about 3 cm. long was made in the midline, and additional incisions about 1 cm. long were made at the posterior part of the head, one for each electrode to be implanted. The scalp was retracted and the preselected points marked with the stereotaxic micromanipulator on the surface of the skull. Burr holes were made at these points, using a 2 mm. diameter dental drill. The dura was punctured and the needle introduced with the micromanipulator to the desired depth. The electrode was then cemented to the bone with Fleck's dental cement (Mizzy, Inc., New York). Allowing a few minutes for the cement to dry the needle electrode was curved over the surface of the skull, and the socket was passed through

Fig. 2
Needle electrodes have been introduced into the brain with a stereotaxic instrument, cemented to the skull and fixed with metallic sutures through the bone.

one of the small openings in the scalp. Two additional burr holes, about 1.5 mm. diameter, spaced about 1 cm. apart, were drilled in the skull, 10 mm. posterior to the entrance of the electrode; one piece of the bare .020" stainless steel wire was led through each hole, the wires were crossed under the skull and brought out the opposite hole, and were then tied over the polyethylene protection of the electrode, which was thus solidly anchored to the skull. The plate electrodes were introduced manually through burr holes (about 5 mm. diameter) and a small slit in the dura. No dental cement was used. Fixation to the skull was similar to that of the needle electrode.

Surgical procedures for cats and dogs were the same, with the difference that the occipital protuberance was used to anchor the electrodes to the skull.

Apparatus. A Hals Delgado two channel stimulator, and two Grass stimulators, model S4A, were used. Stimulations were monitored through a two-beam Du Mont oscilloscope, type 322A. Still and moving pictures were often taken; recordings were made on a Grass 8-channel electroencephalograph, model III D.

Fig. 3

Five months after implantation of 2 plate and 2 needle electrodes, totalling 28 leads. The 2 left side sockets, partly hidden by the hair, are visible at the posterior part of the head.

The brains were usually embedded in paraffin, serially sectioned at 15 μ, and one in each 10 sections stained by Nissl, Spielmeyer, van Gieson or Klüver method.

Post-operative results. Insertion of thin plate electrodes (1 mill) below the dura proved to be uneventful. Insertion of needle electrodes in animals also proved to be safe, even in monkeys with leads in the respiratory center of the medulla. The post-operative course was generally good, and antibiotics were not necessary. Healing of the point of entrance through the skin was sometimes disturbed by plugging in the leads, and occasionally there was a local infection, easily controlled with local antibiotics. The presence of intracerebral leads did not produce detectable changes in behavior, motility, or in performance of psychological tests. However, in a few cases in which rather rigid plates (5 or more mills thick) were used on motor areas, a transient paresis was observed. In about 85 per cent of our series the electrodes were intact until the animals were sacrificed.

Cats and monkeys were stimulated with complete freedom of movement during the performance of different types of tests, such as visual discrimination, delayed alternation, and conditioning avoidance. This freedom was essential to study of behavior and some sensory phenomena.

Study of the brain after electrode implantation. The brains of 75 cats and 63 monkeys, in which electrodes had been implanted for 1 to 14 months, were studied. Rigid plate electrodes, using thick polyethylene (5 or more mills) caused a marked depression on the implantation area. Polyethylene plates of 1 mill thickness produced a small impression on the brain surface, and the protruding balls of the leads were often marked on the cortex. There was a slight glial reaction without observable alteration of the neurons.

Introduction of needle electrodes within the brain substance produced a mechanical destruction along the needle tract with some hemorrhage, in general very small, and a brain reaction with leucocytic infiltration and glial proliferation around the needle tract. In the majority of cases the diameter of the needle tract, after two or more months of implantation, was less than 1 mm. In some monkeys the needle tracts were very small, only about .2 mm. diameter; in a few cases the reaction was more considerable. In most of the animals each point had been repeatedly stimulated for months with uni- or bidirectional square waves, 100 c/sec., 0.2-1 msec. pulse duration. Study of the brain sections did not show histological changes at the point of electrical stimulation.

In 18 monkeys one or several points were electrocoagulated by using 6 mA. DC for about 1¼ min. The extent of brain destroyed with this method was variable. Six of the 18 animals developed encapsulated abscesses, with 3 deaths, 12, 21 and 30 days after coagulation.

Electrical properties of electrodes. Electrodes were tested first in physiological saline prior to implantation, then in the brains of the monkeys during several weeks of implantation, and again in saline immediately after the animals were sacrificed. Voltage/current ratio was essentially linear

for all individual pulse durations and frequencies studied (Mihailovic and Delgado 1955). This suggests that electrical properties of the electrodes did not change during chronic emplacement within organic tissue.

Specificity of responses and spread of current. Specificity of some responses, such as screaming, defensive-offensive behavior, scratching, yawning, etc., was repeatedly observed (Delgado 1952b; 1952c; Delgado and Anand 1953). Each of these responses could be evoked by electrical stimulation of only one or 2 of the 12 to 30 leads implanted in the brain of each animal. As leads 1 mm. apart evoked different responses in some cases it is probable that the area of the brain stimulated by the electrical current was smaller than 1 mm. In some experiments in which intracerebral leads could be moved through needle guides implanted in the skull (Delgado 1955) it was determined that changes of only .5 mm. in the position of the leads could result in dramatic change in response. However, in other cases a similar response could be elicited by stimulation of leads 3 mm., 6 mm., or more, apart.

Excitability. In table I threshold for motor responses during three months of electrode implantation is shown. In this case which was representative, one plate electrode was placed on the motor area of each side (RP and LP), and one needle in diencephalic structures of each side (RN and LN). Voltage and current (mA.) were monitored routinely during *each* stimulation. As we see in this table, threshold intensities in milliamperes were rather constant in most of the points throughout the observation period. Some points had a small increase in threshold, and only one point (LP 1) showed a marked increase after one and a half months of experimentation. Threshold voltage showed some increase after three months of implantation. This suggests that the total impedance increased with time of implantation, but the excitability of the brain was maintained with small variations. Table I also shows that tendency to increased threshold voltage throughout implantation time was greater in the case of needle than in plate electrodes.

TABLE I

THRESHOLDS OF MOTOR RESPONSES DURING 3 MONTHS OF ELECTRODE IMPLANTATION

DAYS	7		14		21		30		45		60		90	
POINT	V	mA	V	mA	V	mA	V	mA	V	mA	V	mA	V	mA
RN_1	1.5	0.25	1.2	0.25	1.5	0.25	2.0	0.30	2.5	0.35	2.0	0.35	2.5	0.35
RN_2	1.5	0.55	1.6	0.45	1.7	0.45	2.0	0.5	2.0	0.45	2.0	0.45	2.5	0.5
RN_3	1.5	0.45	1.5	0.40	1.5	0.4	1.8	0.45	2.5	0.45	2.0	0.45	2.5	0.5
LN_1	2.5	0.6	3.0	0.55	3.0	0.6	3.5	0.65	4.5	0.7	4.0	0.65	4.0	0.65
LN_2	1.5	0.4	2.0	0.4	1.5	0.4	1.5	0.4	2.0	0.4	2.0	0.4	2.5	0.4
LN_3	1.5	0.35	1.5	0.3	1.8	0.35	2.0	0.35	2.5	0.4	2.5	0.4	3.0	0.4
LP_1	2.5	0.75	2.5	0.7	3.0	0.7	3.5	0.8	4.0	1.0	4.5	1.3	4.0	1.2
LP_2	6.0	2.5	6.0	2.3	6.0	2.5	6.0	2.5	6.5	2.0	7.0	2.5	6.5	2.5
LP_3	7.0	2.6	7.0	2.5	6.5	2.5	6.5	2.5	6.0	2.5	6.5	2.5	6.5	2.5
RP_1	4.5	1.6	4.5	1.55	4.0	1.3	4.0	1.3	5.0	2.0	5.5	2.0	5.0	1.8
RP_2	1.8	0.5	2.0	0.5	2.0	0.5	2.0	0.5	2.5	0.6	2.5	0.65	2.5	0.6
RP_3	2.0	0.6	2.0	0.5	2.5	0.7	2.5	0.65	2.5	0.7	2.5	0.65	2.5	0.65

Electrical activity. The spontaneous electrical activity recorded through different leads showed typical patterns at each point, which were repeated with similar characteristics throughout the period of observation. Sometimes these patterns could be considerably changed under the influence of different conditions, for example, noise level of the room, eyes open or closed, etc. If experimental conditions

were the same, the patterns were alike in recordings taken with weeks or months of interval, as shown in figure 4.

Evoked after discharges. After discharge evoked by electrical stimulation of the brain had a typical pattern which repeated itself each time a point was stimulated with appropriate intensities. These patterns were typical for each point but were different in different areas, which suggests a local autonomy of the phenomenon. An example of after discharge evoked in an unanesthetized monkey by monopolar stimulation of point no. 2 of the left needle electrode is shown in figure 5. The needle was placed in the rhinencephalon; the plate was placed over the motor and premotor areas.

COMMENT

With remote controlled stimulation there are no leads piercing the skin, which is a great advantage, but these techniques have the following limitations: (*a*) they cannot be used for recording; (*b*) in general only one point of the brain may be stimulated; (*c*) it is not possible to monitor the stimulation during the experiments and therefore precise data concerning parameters of stimulation are not known; (*d*) intensity of stimulation depends upon the received signal which may vary with changes in the orientation of the receiving system.

In other techniques leads connecting the electrodes implanted in the animals with the experimental

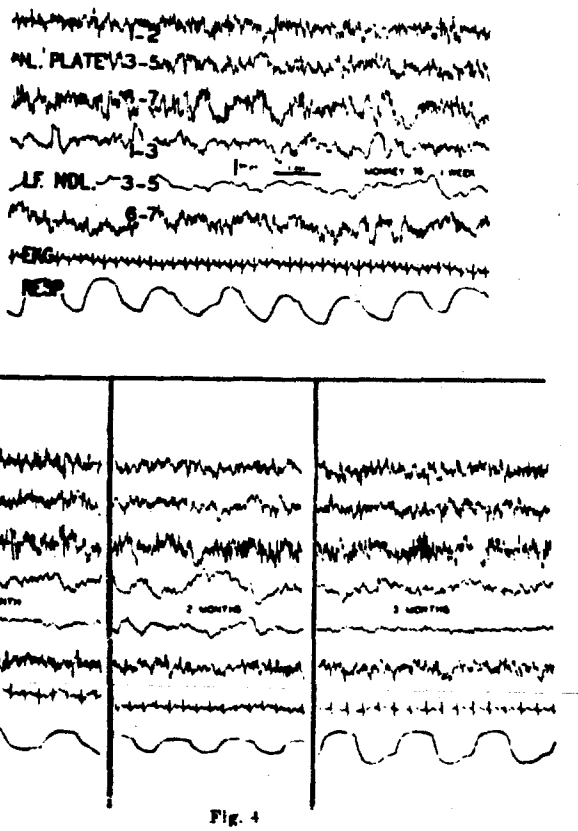

Fig. 4

Patterns of spontaneous electrical activity of each point were similar during the observation period; examples one week, one month, 2 months, and 3 months after implantation.

apparatus are employed. The use of multilead electrodes seems profitable, since with about the same effort and operatory trauma more leads are available. In addition to this, their construction keeps the interlead distances constant, which is a great advantage in comparing electrical recordings of different areas. In some techniques the electrodes are fixed to the skull by means of superstructures, screwed to the bone. In contrast, the use of dental cement and metallic sutures to fix the electrodes to the skull is far less bulky, it is an easier operation, it decreases the accidental breakage of leads, and is less disturbing to the animals.

Implantation of electrodes, even in structures as delicate as the medullary centers, proved to be safe and long term implantation did not seem to affect the health or behavior of the animals. Electrocoagulation was more hazardous. Functionally, there was remarkable constancy of results when similar experiments were performed with months of interval. This was of special interest concerning electrical activity. As there was destruction along the needle

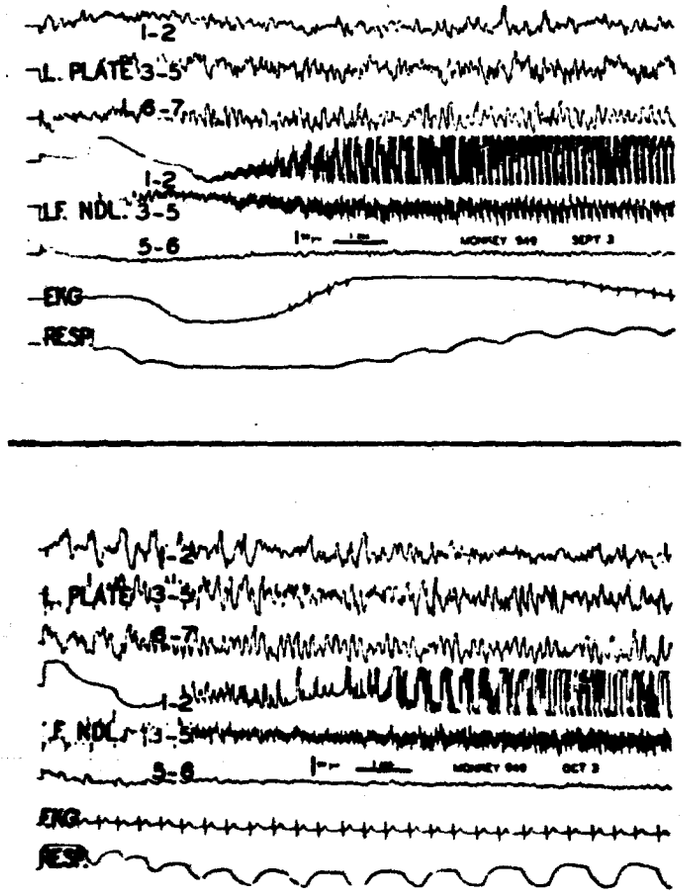

Fig. 5

Examples of after discharges showing similar patterns, evoked by stimulation of the same point with one month of interval.

tracts the recorded activity could represent the disturbance produced by the insertion of the electrodes, rather than the "normal" spontaneous activity of the brain. However, the following arguments do not support this possibility: (*a*) signs of irritation, such as spikes, were in general absent in recordings; (*b*) patterns of electrical activity were different in different areas, which suggests that local activity was being recorded, and not a common "lesion" activity; (*c*) patterns of electrical activity of each point had similar characteristics in recordings taken with months of interval; (*d*) activity recorded through needle electrodes varied according to the anatomical location, but did not show specific differences from the activity recorded through plate electrodes. It would seem that, even if the presence of electrodes could produce some alteration of the brain, *the experimental conditions remained constant during the several months of observation.*

SUMMARY

1. Techniques of construction and implantation of multilead electrodes in the brain of animals are described. Technical problems of implantation are examined.

2. No operatory accidents occured, and no deficits were produced by electrode insertion.

3. After several months of implantation, plate electrodes produced a small impression on the brain surface without histological alteration of the neurons. Damage of the brain resulting from needle electrodes was generally less than 1 mm. in diameter. Infections were rare. Electrocoagulation was more hazardous.

4. Prolonged electrical stimulation of the brain did not cause any detectable local histological changes.

5. Cerebral stimulation was possible in cats and monkeys which had freedom of movement. This permitted studies concerning behavior, sensory phenomena, correlations between clinical manifestations and electrical activity of the brain, and also psychological testing of the animals.

6. Patterns of response evoked by electrical stimulation proved to be typical for each point, and reliable through time.

7. Thresholds of electrical stimulation proved to be rather constant throughout the months of observation.

8. "Spontaneous" electrical activity and patterns of evoked post discharges recorded by means of implanted electrodes were similar in recordings taken with weeks or months of interval.

9. Conclusions 6, 7, and 8 indicate that the presence of electrodes disturbs the brain activity very little, or at least, that the experimental conditions do not change during the period of observation.

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